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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,845	05/11/2001	Wayne Godfrey	16524.010	7084

28381 7590 07/16/2002

ARNOLD & PORTER
IP DOCKETING DEPARTMENT; RM 1126(b)
555 12TH STREET, N.W.
WASHINGTON, DC 20004-1206

EXAMINER

BELYAVSKIY, MICHAEL A

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/852,845

Applicant(s)

GODFREY ET AL.

Examiner

Michail A Belyavskiy

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 May 2001 and 29 April 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31,33,35 and 59-77 is/are pending in the application.
- 4a) Of the above claim(s) 73-77 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31,33,35 and 59-72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

1. Applicant's amendment, filed 4/29/02 (Paper No. 6), is acknowledged.
Claims 26 and 27 have been canceled. Claims 1-25, 27-30, 36-58 have been canceled previously.
Claims 31, 33, 35 and 59-77 are pending.
2. This application is a continuation of 08/472940, US Pat. NO: 6,277962. The specification on page 1 should be amended to reflect the status of the parent application, serial number 08/472940.
3. Applicant's election with traverse of Group I (Claims 31, 33, 35 and 59-72) in Paper No. 6 is acknowledged. The traversal is on the ground(s) that (1) the groups of inventions are not independent since antibodies of Group I are related to and used with methods of Groups II and III, and (2) the examination of the entire application would not constitute a burden to search. This is not found persuasive because with respect to point (1) above, the inventions are distinct as noted in the last Office Action, as shown by the distinctness described therein. Applicant's attention is directed to MPEP 806.05. With respect to point (2) above, the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the examiner by the examination Groups. The Inventions are distinct for reasons elaborated in paragraphs 3-5 of the previous Office Action.

The requirement is still deemed proper and is therefore made FINAL.
4. Claims 73-77 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 31, 33, 35 and 59-72 are under consideration in the instant application.
5. Sequence compliance: The instant application is in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

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6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed*.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 31, 33, 35 and 59-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

10. It is apparent that L 106 antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines which produce these antibodies. See 37 CFR 1.801-1.809.

While it is noted that Applicant has indicated that the hybridoma producing the L-106 antibody was deposited with the ATCC on HB11483; the following requirements must still be met in order to fulfill the requirements of 37 CFR 1.801-1.809. (See also MPEP 2402-2411.)

If the deposit have been made under the terms of the Budapest treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma producing the L-106 antibody has been deposited under the Budapest Treaty and that the hybridoma producing the L-106 antibody will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer. See 37 CFR 1.806.

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If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in position to make such assurances, or statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met

Amendment of the specification to disclose the date of the deposit and complete name and address of the depository is required

11. Furthermore, specification disclosed a humanized antibody comprising a humanized heavy chain, wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody heavy chain and humanized antibody comprising humanized light chain, wherein the humanized light chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody light chain that specifically binds to an ACT-4-h-1 receptor polypeptide. The specification does not provide any guidance as to how make *any* humanized antibody comprising a humanized heavy chain wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody heavy chain as recited in Claim 64, or *any* humanized antibody comprising humanized light chain wherein the humanized light chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody light chain as recited in Claim 67 or *any* humanized light chain wherein the humanized light chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody light chain and humanized heavy chain wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody heavy chain, recited in Claim 70.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to make and use "*any* humanized antibody comprising a humanized heavy chain wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody heavy chain as recited in Claim 64, or *any* humanized antibody comprising humanized light chain wherein the humanized light chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody light chain as recited in Claim 67 or *any* humanized light chain wherein the humanized light chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody light chain and humanized heavy chain wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody heavy chain, recited in Claim 70 without teaching for what antigen they would be specific.

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The specification does not provide sufficient guidance as to which antigen, besides ACT-4-h-1 receptor polypeptide, these antibody would be specific. Colman *et al.* in Research in Immunology (145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al.* in Journal of Protein Chemistry (11(5):433-444, 1992) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Futher, Lederman *et al.* in Molecular Immunology (28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Additionally, Li *et al.* in PNAS (77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

Because of this lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo *et al.* in the Protein Folding problem and Tertiary Structure prediction, 1994, Merz *et al.*, (ed), Birkhauser, Boston, MA, pp.433 and 492-495), it would require an undue amount of experimentation for on of skill in the art to arrive at the claimed humanized antibody comprising a humanized heavy chain wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complimentarity determining region of an L 106 antibody heavy chain , or humanized antibody comprising humanized light chain wherein the humanized light chain comprises three complementarity determining regions corresponding to the complimentarity determining region of an L 106 antibody light chain.

The scope of the claimed antibody is not commensurate with the enablement provided by the disclosure of antibody that specifically binds to an ACT-4-h-1 receptor polypeptide, with regard to the extremely large number of antibody broadly encompassed by the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention

12. Claims 64, 67, 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following *written description* rejection is set forth herein.

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Applicant is in possession humanized antibody comprising a humanized heavy chain, wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody heavy chain and a humanized light chain, wherein the humanized light chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody light chain that specifically binds to an ACT-4-h-1 receptor polypeptide, however, Applicant is not in possession of *any* humanized antibody comprising a humanized heavy chain wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody heavy chain as recited in Claim 64, or *any* humanized antibody comprising humanized light chain wherein the humanized light chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody light chain as recited in Claim 67 or *any* humanized light chain wherein the humanized light chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody light chain and humanized heavy chain wherein the humanized heavy chain comprises three complementarity determining regions corresponding to the complementarity determining region of an L 106 antibody heavy chain, recited in Claim 70.

Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of antibody may be achieved by means of a recitation of a specific antigen with which these antibody are binding, or of a recitation of structural and functional features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 “Written Description” Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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14. Claims 31, 60, 64, 65, 67, 68 70, 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31, 60, 64, 65, 67, 68 70, 71 are indefinite in the recitation of "L106 antibody" because its characteristics are not known. The use of " L106 antibody " as the sole means of identifying the claimed antibody and hybridoma renders the claim indefinite because " L106 antibody " is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct hybridoma.

Applicant should amend the claim to provide a ATCC deposit accession number to clearly define the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 31, 59 and 62 are rejected under 35 U.S.C.102(b) as being anticipated by Knapp et al. (Leucocyte Typing IV,1989).

Knapp et al. teach the same L106 antibody (Table 4, page 391, or Table 1, page 482 in particular).

The reference teachings anticipate the claimed invention.

However, Applicant's attention is pointed to MPEP 2133.03 (e) (4) and (5). Applicants is invited to provide evidences that samples containing the L106 antibody were for experimental purpose and were under Applicant's supervision, control and restrain on subsequent use.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp et al. (Leucocyte Typing IV, 1989) in view of Thorpe et al. (Immunological Rev., 1982).

Knapp et al. has been discussed supra.

The claimed invention differs from the reference teaching only by the recitation of immunotoxin comprising L106 antibody fused to a toxin polypeptide .

Thorpe et al. teach immunotoxin by linking toxins to antibodies in order to attack tumor cells (see entire document, page 119 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to generate immunotoxin taught by Thorpe et al. using the antibody taught by Knapp et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody could be used to target toxins to tumor cells as taught by Thorpe et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claims, 35, 60, 61 and 64-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp et al. (Leucocyte Typing IV, 1989) in view of Owens *et al* (J.of Immunol.. Method. 1994) and Bird *et al* (Science, 1988)..

The teachings of Knapp et al. have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a fragment of the L106 (Claims 35 and 60), heavy chain of L106 antibody, light chain of L106 antibody, Fab fragment antibody, Fab' fragment antibody, F(ab')₂ fragment antibody, Fabc fragment antibody, Fv fragment antibody (Claim 61) and fragment of humanized L106 antibody (Claim 66).

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Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')₂ fragment or a humanized antibody, monoclonal antibody technology including, chimeric, single chain, Fab fragments, and F(ab')₂. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement - dependent cytotoxicity (see the entire document).

Bird *et al* teach a single chain antigen binding proteins composed of an antibody variable light - chain amino acid sequence (V_L) tethered to a variable heavy -chain sequence (V_H) by a designed peptide that links the carboxyle terminus of the V_L sequence to the amino terminus of the V_H sequence. Bird *et al* further teach that the single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion (see the entire document and page 426, left column, 2nd paragraph in particular)).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use L106 antibody taught by Knapp *et al.* to make a fragment of the L106 antibody; a heavy chain of L106 antibody; a light chain of L106 antibody, a Fab fragment antibody, a Fab' fragment antibody, a F(ab')₂ fragment antibody, a Fabc fragment antibody, a Fv fragment antibody, a fragment of humanized L106 antibody, a humanized antibody, a Fab and F(ab')₂ fragments taught by Owens *et al.* or as a single chain antibody as taught by the Bird *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxicity as taught by Owens *et al.* and because single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion as taught by Bird *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.


20. No claim is allowed.

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21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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July 5 2002


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